THE GENETIC COVARIANCE BETWEEN CHARACTERS MAINTAINED BY PLEIOTROPIC MUTATIONS

RUSSELL LANDE[1]

Laboratory of Genetics, University of Wisconsin, Madison, Wisconsin

Manuscript received November 14, 1978
Revised copy received May 31, 1979

ABSTRACT

A statistical genetic model of a multivariate phenotype is derived to investigate the covariation of pleiotropic mutations with additive effects under the combined action of phenotypic selection, linkage and the mating system. Equilibrium formulas for large, randomly mating populations demonstrate that, when selection on polygenic variation is much smaller than twice the harmonic mean recombination rate between loci with interacting fitnesses, linkage disequilibrium is negligible and pleiotropy is the main cause of genetic correlations between characters. Under these conditions, approximate expressions for the dynamics of the genetic covariances due to pleiotropic mutations are obtained. Patterns of genetic covariance between characters and their evolution are discussed with reference to data on polygenic mutation, chromosomal organization and morphological integration.

THE course of evolution of the average phenotype in a population in response to natural or artificial selection is determined by the additive genetic vari- and covariances between characters. If an individual organism is represented by a column vector $\mathbf{z}$ of polygenic traits $z_1, \ldots, z_m$ with additive genetic and environmental components following independent multivariate normal distributions, the change per generation in the vector of mean phenotypes from selection is (LANDE 1979a)

$$\Delta\bar{\mathbf{z}} = \mathbf{G} \nabla \ln\bar{W} \ . \tag{1}$$

$\mathbf{G}$ is the matrix of additive genetic variances and covariances of the characters and $\nabla\ln\bar{W}$ is the gradient vector of the natural logarithm of the mean fitness in the population, or simply the "selection gradient" with respect to changes in $\bar{\mathbf{z}}$. The vector of average phenotypes does not evolve in the direction that produces the maximum rate of increase in mean fitness, which would be along the selection gradient, $\nabla\ln\bar{W}$ (APOSTOL 1962, pp. 175–179). Its direction and speed are governed by the genetic covariance matrix and the selection gradient. The present study concerns the factors that determine the genetic covariance matrix, $\mathbf{G}$, in large randomly mating populations. Nonrandom systems of mating will be analyzed in a separate paper.

[1] Present address: Department of Biophysics and Theoretical Biology, The University of Chicago, 920 East 58th Street, Chicago, Illinois 60637.

Genetic covariance between traits in a randomly mating population can be maintained in two ways: through genes with pleiotropic (multiple) effects, and by linkage disequilibrium (statistical nonindependence) between alleles at distinct loci affecting different characters. Linkage and pleiotropy are ubiquitous properties of genetic systems. Most eukaryotes have thousands of genes linked together in no more than several dozen chromosomes. Pleiotropic mutations have been discovered in virtually every organism that has been investigated genetically (CASPARI 1952). In fact, pleiotropy may be the rule rather than the exception among mutations (GAUL 1961; WRIGHT 1968, pp. 60–61).

The nature and extent of pleiotropy have been studied in both metrical traits and biochemical systems. For quantitative characters, which are usually influenced by several genes of small effect masked by environmental noise, it is easiest to observe the effects of the new mutations in a homozygous genetic background; this also minimizes the chance of mistaking the segregation of tightly linked loci with independent effects for a single locus with multiple effects. DOBZHANSKY and HOLTZ (1943) induced mutations in an inbred line of *Drosophila melanogaster* at the white-eye and yellow-body loci and found that almost all influenced spermatheca shape. SPRAGUE, RUSSELL and PENNY (1960) and RUSSELL, SPRAGUE and PENNY (1963) estimated that among spontaneous minor mutations affecting nine vegetative and seed characters in doubled monoploid and long-inbred lines of maize, roughly one-fourth to one-half of the total character changes were due to pleiotropy. Multiple effects associated with a mutant can be confidently attributed to a single gene when their expression can be traced backwards through developmental or biochemical pathways to a common cause. Skeletal mutations of the mouse and human biochemical defects have been particularly well studied in this respect (GRÜNEBERG 1963; HARRIS 1970). The pleiotropic effects of a mutant gene usually originate from one primary developmental or biochemical perturbation that affects different characters either directly or through compensatory changes in other systems. Causal connections between manifold effects of a gene are often unknown, and some may be truly autonomous, as can be demonstrated using mosaics (STERN and TOKUNAGA 1968).

Pleiotropic effects of a mutation often display substantial independence in their manifestation. The degree of dominance and penetrance may differ among the traits affected, depending on the environment and the genetic background. Distinct effects of the same allele are capable of separate modification by artificial selection, and multiple alleles of a locus sometimes differ not only in the intensity of the syndromes they produce, but also in the relative involvement of the various characters (CASPARI 1952; GRÜNEBERG 1963, pp. 2–17).

Since quantitative characters generally are polygenic and a large fraction of all mutations are pleiotropic, different loci must often influence overlapping sets of characters. The perusal of any extensive list of mutant phenotypes amply supports this view, *e.g.*, on *Drosophila* see LINDSLEY and GRELL (1968) and BRAVER (1956), and on mice consult GREEN (1975, pp. 87–150, 329–336). Shared specificities of pleiotropic effects between loci are also revealed by abundant biochemical evidence (*e.g.*, HADORN 1956; HARRIS 1970; SINGH 1976). Groups

of loci with overlapping pleiotropic effects often result from originally identical duplicate genes that have evolved some specificity of expression in certain tissues, developmental stages and/or biochemical reactions. These may be unlinked, if they arose from a polyploidy event, or tightly linked, if they occurred by tandem duplication; many examples of each are known (HARRIS 1970; OHNO 1970). Thus, a complete genetic system consists of many linked genes with multiple overlapping effects, and there are usually enough genetic degrees of freedom in a large stable population so that artificial selection on almost any character gives a direct response, as well as changes in many genetically correlated characters (WRIGHT 1977, pp. 234, 283–288).

Studies of morphological integration, as measured by phenotypic covariance patterns (*e.g.*, KURTÉN 1953; OLSON and MILLER 1958; BERG 1960; BADER and HALL 1960), have shown that high phenotypic correlations between characters are associated with functional relationship, homology and contiguity (Pearson's rule of neighborhood). However, these categories are not mutually exclusive in their occurrence, nor in terms of the causal mechanisms of variation involved. A common situation where function, homology and contiguity all enter is that of meristic characters such as limbs, digits, vertebrae, ribs, teeth and flower parts. Duplication of genes affecting a repeated developmental field allows specialization and localization of gene action, enabling morphological specialization to occur (OHNO 1970). The tremendous interspecific diversity into which such polygenic meristic characters have evolved since their origins as undifferentiated series (*e.g.*, ROMER 1966), as well as divergence in their covariance patterns among populations, also attests to the great adaptability of character complexes influenced by many genes with overlapping pleiotropic effects in response to changing selective regimes.

The genetic covariance structure for the traits of a population with such a complex genetic system results from a balance of forces, including pleiotropic mutation, recombination, selection and the mating system. A statistical model of an entire genome, and the multivariate phenotype that it controls, is derived here to investigate the role of these factors in maintaining the genetic covariance between characters which determines the course of phenotypic evolution (eq. 1). The model also helps to elucidate the evolutionary dynamics of genetic covariance patterns.

THE GENETIC SYSTEM

For simplicity, it is assumed that the genetic and environmental effects are additive for all traits. Polygenic variation can often be rendered largely additive by proper choice of measurement scales (WRIGHT 1952; FALCONER 1960, Chapter 17). With additivity on an underlying scale, simple forms of dominance and interaction due to threshold expression of traits can also be encompassed by this scheme (FISHER 1930, pp. 111–115; WRIGHT 1934; GREEN 1962; GRÜNEBERG 1963, pp. 3–17).

The pleiotropic effects of an allele from the maternal and paternal gamete at

locus i on a set of m phenotypic traits are denoted, respectively, as column vectors (with superscript ^{T} indicating transpose)

$$\mathbf{x}_i = (x_{i1}, \ldots, x_{im})^T \text{ and } \mathbf{x'}_i = (x'_{i1}, \ldots, x'_{im})^T \ . \tag{2}$$

The vector of phenotypic measurements on an individual organism is

$$\mathbf{z} = (z_1, \ldots, z_m)^T \ , \tag{3a}$$

and, separating this into genetic and environmental effects, the additivity assumption is

$$\mathbf{z} = \mathbf{g} + \mathbf{e} = \sum_{i=1}^{n} (\mathbf{x}_i + \mathbf{x'}_i) + \mathbf{e} \ , \tag{3b}$$

where the summation extends over all n loci.

Writing the allelic effects as deviations from their means,

$$\mathbf{y}_i = \mathbf{x}_i - \bar{\mathbf{x}}_i \text{ and } \mathbf{y'}_i = \mathbf{x'}_i - \bar{\mathbf{x}}'_i \ , \tag{4a}$$

in the absence of sexual dimorphism, the covariance matrix of manifold effects of alleles at loci i and j from the same gamete is defined for a population as the expectation

$$\mathbf{C}_{ij} = \mathrm{E}[\mathbf{y}_i \mathbf{y}_j^T] = \mathrm{E}[\mathbf{y'}_i (\mathbf{y'}_j)^T] \tag{4b}$$

When $i = j$, $\mathbf{C}_{ii}$ is the covariance matrix of pleiotropic effects at locus i, while for $i \neq j$, $\mathbf{C}_{ij}$ is the matrix of covariances between allelic effects due to linkage disequilibrium. The covariance matrices for the effects of alleles from different gametes, determined by the mating system, are defined by

$$\mathbf{C'}_{ij} = \mathrm{E}[\mathbf{y}_i (\mathbf{y'}_j)^T] = \mathrm{E}[\mathbf{y'}_i \mathbf{y}_j^T] \ . \tag{4c}$$

Assuming no genotype-environment correlations, the covariance matrix for the phenotypic traits, $\mathbf{P}$, can be written as a sum of the genetic and environmental covariance matrices

$$\mathbf{P} = \mathrm{E}[(\mathbf{g} - \bar{\mathbf{g}})(\mathbf{g} - \bar{\mathbf{g}})^T] + \mathrm{E}[\mathbf{e}\mathbf{e}^T] = \mathbf{G} + \mathbf{E} \ . \tag{5}$$

Without loss of generality, we take $\bar{\mathbf{e}} = \mathbf{0}$. From (5) and (3b), the genetic covariance matrix for the traits can be expressed as a sum of the covariance matrices for all pairs of alleles in the zygotes

$$\mathbf{G} = 2 \sum_{i=1}^{n} \sum_{j=1}^{n} (\mathbf{C}_{ij} + \mathbf{C'}_{ij}) \ . \tag{6}$$

Although $\mathbf{C}_{ij}$ and $\mathbf{C'}_{ij}$ are generally not symmetric for $i \neq j$, $\mathbf{C}_{ij} = \mathbf{C}^T_{ji}$ and $\mathbf{C'}_{ij} = (\mathbf{C'}_{ji})^T$, which is consistent with the symmetry of $\mathbf{G}$.

Recombination: The linkage map of the loci is permitted to have any configuration with positive recombination rates between all pairs of loci, $r_{ij} > 0$ for $i \neq j$ and $r_{ii} = 0$.

Mutation: A wide range of possible allelic effects is postulated for each locus for the traits it influences. Mutation is assumed to occur at an equal rate and to produce the same distribution of changes in effects for all alleles at a locus,

although these parameters may differ between loci. Let $\mathbf{a}_i$ signify the vector of mutational changes in allelic effects at locus i during one generation, including the nonmutant class. With μ_i as the mutation rate per generation and $\mathbf{b}_i$ as the vector of *mutant* changes at locus i, the mean change per generation in allelic effect is

$$\mathbf{a}_i = (1-\mu_i)\mathbf{0} + \mu_i\bar{\mathbf{b}}_i = \mu_i\bar{\mathbf{b}}_i \ , \tag{7a}$$

and the covariance matrices between allele effects at different loci within gametes after mutation are, using (4)

$$\mathrm{E}[(\mathbf{y}_i+\mathbf{a}_i)(\mathbf{y}_j+\mathbf{a}_j)^T] - \bar{\mathbf{a}}_i\bar{\mathbf{a}}_j^T = \mathbf{C}_{ij} \text{ for } i\neq j \ , \tag{7b}$$

since $\mathrm{E}[\mathbf{y}_i\mathbf{a}_j^T] = \mathbf{0}$ and $\mathrm{E}[\mathbf{a}_i\mathbf{a}_j^T] = \mathbf{a}_i\mathbf{a}_j^T$ for $i\neq j$. For the pleiotropic effects at a single locus, the left side of (7b) with $i=j$ becomes

$$\mathbf{C}_{ii} + \mathrm{E}[\mathbf{a}_i\mathbf{a}_i^T] - \bar{\mathbf{a}}_i\bar{\mathbf{a}}_i^T \ .$$

It is more revealing to partition these pleiotropic covariances into the average covariances within nonmutant and mutant groups of alleles in the population,

$$(1-\mu_i)\mathbf{C}_{ii} + \mu_i\{\mathbf{C}_{ii} + \mathrm{E}[(\mathbf{b}_i-\bar{\mathbf{b}}_i)(\mathbf{b}_i-\bar{\mathbf{b}}_i)^T]\}$$

plus the covariation between the means of these two groups, $\mu_i(1-\mu_i)\mathbf{b}_i\mathbf{b}_i^T$, giving a total change from $\mathbf{C}_{ii}$ of

$$\mathbf{U}_i = \mu_i\,\mathrm{E}[(\mathbf{b}_i-\bar{\mathbf{b}}_i)(\mathbf{b}_i-\bar{\mathbf{b}}_i)^T] + \mu_i(1-\mu_i)\bar{\mathbf{b}}_i\bar{\mathbf{b}}_i^T \ . \tag{7c}$$

The covariances between loci from linkage disequilibrium are unchanged by mutation (eq. 7b), while the pleiotropic covariances are augmented both by the dispersion and directionality of the mutational changes, except when $\mu_i=1$ (eq. 7c). The influence of mutation on $\mathbf{C}_{ij}$ can thus be written as an additive contribution $\delta_{ij}\mathbf{U}_i$, where $\mathbf{U}_i$ is the constant symmetric matrix in (7c) and $\delta_{ij}=1$, if $i=j$, and zero otherwise. The mutation matrices, $\mathbf{U}_i$, will usually be singular, since each locus does not affect all characters, and the pleiotropic effects of multiple alleles at a locus may be strictly proportional (statistically dependent).

This mutation model entails a constant rate of production of additive genetic variance and covariance between traits, irrespective of the background level of genetic variation in the population, which seems consistent with experimental studies on artificial mutagenesis in homozygous and heterozygous strains (review in LANDE 1977). It is a generalization of a mutation process introduced by KIMURA (1965) for a single polygenic character.

Selection: In a large population with discrete generations where selection on adults is followed by mating, recombination, mutation and reproduction, the method of LANDE (1977) for a single polygenic character can be extended to multiple characters. The dynamic equation for the genetic covariance structure, measured in the juvenile stage, appears as

$$\mathbf{C}_{ij}(t+1) = (1-r_{ij})[\mathbf{C}_{ij}(t)]_w + r_{ij}[\mathbf{C}'_{ij}(t)]_w + \delta_{ij}\mathbf{U}_i \ . \tag{8}$$

This is not a complete recursion system until the covariance matrices after selec-

tion. designated by the subscript w, can be expressed in terms of those before selection. To evaluate the results of selection, consider the matrix formulation of conditional covariance for multivariate normal distributions (*cf.*, KENDALL and STUART 1973, Chapter 27),

$$\mathbf{C}_{ij} = \mathbf{B}_i\mathbf{P}\mathbf{B}_j^T + \mathbf{C}_{ij\cdot z} \ . \tag{9a}$$

The last term is the residual covariance matrix $\mathbf{x}_i$ with $\mathbf{x}_j$ for fixed $\mathbf{z}$, and $\mathbf{B}_i$ is a matrix of partial regresssion coefficients of $\mathbf{x}_i$ on $\mathbf{z}$,

$$\mathbf{B}_i = \mathbf{C}_{i,z}\mathbf{P}^{-1} \tag{9b}$$

with

$$\mathbf{C}_{i,z} = \mathrm{E}[(\mathbf{x}_i - \bar{\mathbf{x}}_i)(\mathbf{z}_i - \bar{\mathbf{z}})^T] = \sum_{j=1}^{n} (\mathbf{C}_{ij} + \mathbf{C}'_{ij}) \ . \tag{9c}$$

The genetic covariance matrix of the characters can be expressed from (6) and (9c) as

$$\mathbf{G} = 2\sum_{i=1}^{n} \mathbf{C}_{i,z} \ . \tag{10}$$

Postulating that selection acts only on the phenotypic traits, with individuals of phenotype $\mathbf{z}$ having fitness $W(\mathbf{z})$, a useful relation is that neither the matrix of partial regression coefficients, $\mathbf{B}_i$, nor the residual genetic covariances for fixed $\mathbf{z}$, $\mathbf{C}_{ij\cdot z}$, are altered by selection, although all of the covariance matrices $\mathbf{C}_{ij}$ may change (PEARSON 1903; HAZEL 1943; COCHRAN 1951). Thus, after selection

$$[\mathbf{C}_{ij}]_w = \mathbf{B}_i[\mathbf{P}]_w\mathbf{B}_j^T + \mathbf{C}_{ij\cdot z} \ . \tag{11}$$

This remarkable fact can be intuited geometrically by visualizing the regression equations $\mathbf{x}_i - \bar{\mathbf{x}}_i = \mathbf{B}_i(\mathbf{z} - \bar{\mathbf{z}}) + \mathbf{x}_{i\cdot z}$ and considering phenotypic selection as weighting the distributions of residual variation in $\mathbf{x}_i$ for different values of $\mathbf{z}$, $\mathbf{x}_{i\cdot z}$. Since the residuals are homoscedastic with zero means, evidently such weighting does not distort the residual variation or the regression functions. Employing (9a) to eliminate $\mathbf{C}_{ij\cdot z}$ from (11) gives

$$[\mathbf{C}_{ij}]_w = \mathbf{C}_{ij} - \mathbf{B}_i(\mathbf{P} - [\mathbf{P}]_w)\mathbf{B}_j^T \tag{12a}$$

and similarly for the effects of alleles at loci i and j from complementary gametes.

$$[\mathbf{C}'_{ij}]_w = \mathbf{C}'_{ij} - \mathbf{B}_i(\mathbf{P} - [\mathbf{P}]_w)\mathbf{B}_j^T \ . \tag{12b}$$

Substituting these into (8) produces

$$\Delta\mathbf{C}_{ij} = -r_{ij}(\mathbf{C}_{ij} - \mathbf{C}'_{ij}) - \mathbf{B}_i(\mathbf{P} - [\mathbf{P}]_w)\mathbf{B}_j^T + \delta_{ij}\mathbf{U}_i \ . \tag{13}$$

A Gaussian fitness function can be used to approximate many forms of weak stabilizing selection in the vicinity of an optimum phenotype vector, $\hat{\mathbf{z}}$,

$$W(\mathbf{z}) = \exp\{-(1/2)(\mathbf{z} - \hat{\mathbf{z}})\mathbf{W}^{-1}(\mathbf{z} - \hat{\mathbf{z}})^T\} \tag{14a}$$

where $\mathbf{W}$ is a positive definite symmetric matrix. Then, if $\mathbf{z}$ is multivariate normal, it can be verified directly or by series expansion that

$$[\mathbf{P}]_w = (\mathbf{P}^{-1} + \mathbf{W}^{-1})^{-1} = \mathbf{P} - \mathbf{P}(\mathbf{W} + \mathbf{P})^{-1}\mathbf{P} \ ,$$

and with (9b) the change in $\mathbf{C}_{ij}$ from selection in equation (13) is

$$-\mathbf{C}_{i,z}(\mathbf{W}+\mathbf{P})^{-1}\mathbf{C}^{T}_{j,z}\ , \tag{14b}$$

which is independent of the mean genetic effects. The preceding calculations are thus valid even if the optimum phenotype, $\hat{\mathbf{z}}$, fluctuates with time.

In a constant environment with $\hat{\mathbf{z}}$ fixed, the eventual equilibrium of the mean phenotype, $\bar{\mathbf{z}}$, may differ from the optimum because of directional mutation pressure. Equilibrium is attained when the change from selection (eq. 1) cancels that from directional mutation at all loci (eq. 7a),

$$\mathbf{G}\nabla \ln \overline{W} = -2\sum_{i=1}^{n} \bar{\mathbf{a}}_i \equiv -\bar{\mathbf{a}}\ . \tag{15a}$$

The final discrepancy between the mean phenotype and the optimum for the Gaussian fitness function is

$$\bar{\mathbf{z}} - \hat{\mathbf{z}} = (\mathbf{W}+\mathbf{P})\mathbf{G}^{-1}\bar{\mathbf{a}}\ . \tag{15b}$$

Although the mean phenotypes or genotypes of the traits converge to an equilibrium, there may be considerable indeterminacy in the mean effects of the individual loci if the number of degrees of freedom for changing allelic effects at all loci exceeds the number of linearly independent adaptive characters, thus allowing substantial random genetic drift among genotypes without altering the distribution of phenotypes or the additive variation for the characters (*cf.*, LANDE 1976).

Random mating: There is no covariance between the effects of alleles in uniting gametes under random mating, $\mathbf{C}'_{ij} = \mathbf{0}$. Using (9c), (13) and (14), the dynamics of the genetic covariances become

$$\Delta\mathbf{C}_{ij} = -r_{ij}\mathbf{C}_{ij} - \mathbf{C}_{i,z}(\mathbf{W}+\mathbf{P})^{-1}\mathbf{C}^{T}_{j,z} + \delta_{ij}\mathbf{U}_i \text{ with } \mathbf{C}_{i,z} = \sum_{j=1}^{n} \mathbf{C}_{ij}\ . \tag{16}$$

A solution of this system of matrix equations must satisfy the symmetry conditions $\mathbf{C}_{ij} = \mathbf{C}^{T}_{ji}$. Here, we seek an approximate solution and conditions when pleiotropy predominates in determining the genetic covariances between characters, and linkage disequilibrium makes minor contributions. It is anticipated this will occur when loci with interacting fitnesses are loosely linked and selection on the genotype is weak (WRIGHT 1969, pp. 72–105, 477), although the form of both the conditions and the solution remain to be found. Furthermore, the precise analysis by FLEMING (1979) of a particular case of this process (with $\mathbf{U}_i$ of rank 1 and $\bar{\mathbf{b}}_i = \mathbf{0}$) indicates that the normality assumptions of equations (9a) and (12a) are most accurate with weak selection.

The off-diagonal equations in (16) at equilibrium have the solution

$$\mathbf{C}_{ij} = -\mathbf{C}_{i,z}(\mathbf{W}+\mathbf{P})^{-1}\mathbf{C}^{T}_{j,z}/r_{ij} \text{ for } i \neq j\ . \tag{17}$$

A condition for linkage disequilibrium to constitute a small part of the expressed genetic variability is

$$\mathbf{x}^{T}\mathbf{G}\mathbf{x} >> 2\mathbf{x}^{T}\sum_{i\neq j}\sum \mathbf{C}_{ij}\mathbf{x} \text{ for all } \mathbf{x}\neq\mathbf{0}\ .$$

Assuming that every character is polygenic and that $\mathbf{C}_{i,z}(\mathbf{W}+\mathbf{P})^{-1}\mathbf{C}^{T}_{j,z}$ among

pairs of loci is nearly independent of r_{ij}, a small contribution can be added on the right, $2\mathbf{x}^T\sum_i \mathbf{C}_{i,z}(\mathbf{W}+\mathbf{P})^{-1}\mathbf{C}^T{}_{i,z}\mathbf{x}/\hat{r}$ where $\hat{r}$ is the harmonic mean recombination rate between loci with interacting fitness ($\mathbf{C}_{ij} \neq \mathbf{0}$), and using (10) this yields $\mathbf{x}^T\mathbf{G}\mathbf{x} >> \mathbf{x}^T\mathbf{G}(\mathbf{W}+\mathbf{P})^{-1}\mathbf{G}\mathbf{x}/2r$ for all $\mathbf{x} \neq \mathbf{0}$. Applying the transformation $\mathbf{x}^* = \mathbf{G}^{1/2}\mathbf{x}$ produces the condition

$$\lambda_{\max} = \max_{\mathbf{x}^*} \frac{\mathbf{x}^{*T}\mathbf{G}^{1/2}(\mathbf{W}+\mathbf{P})^{-1}\mathbf{G}^{1/2}\mathbf{x}^*}{\mathbf{x}^{*T}\mathbf{x}^*} << 2\hat{r} \ . \tag{18}$$

The positive real number $\lambda_{\max}$ is the largest eigenvalue of the matrix in (18) or of $(\mathbf{W}+\mathbf{P})^{-1}\mathbf{G}$ or its transpose, since these are all similar matrices having equivalent eigenvalues (GANTMACHER 1960, pp. 147–128, 310–322). With free recombination, $\hat{r} = 1/2$, this is simply a condition for weak selection on the genetic variation of all characters (and their linear combinations), with tighter linkage requiring weaker selection.

Under weak selection on the genotypes, $\mathbf{W}+\mathbf{P} \simeq \mathbf{W}+\mathbf{E} \equiv \tilde{\mathbf{W}}$, when linkage disequilibrium can be neglected, $\mathbf{C}_{i,z} \simeq \mathbf{C}_{ii}$, the dynamics of the covariance matrix of pleiotropic effects at each locus can be approximated in continuous time from (16) by the equation

$$\frac{d\mathbf{C}_{ii}}{dt} \simeq -\mathbf{C}_{ii}\tilde{\mathbf{W}}^{-1}\mathbf{C}_{ii} + \mathbf{U}_i \ . \tag{19}$$

If $\tilde{\mathbf{W}}$ is non-singular, there exists a non-singular matrix $\mathbf{Q}_i = \mathbf{K}_i{}^T\tilde{\mathbf{W}}^{-1/2}$ where $\mathbf{K}_i$ is an orthogonal unitary matrix ($\mathbf{K}_i{}^T = \mathbf{K}_i{}^{-1}$) which can be chosen such that

$$\mathbf{Q}_i\tilde{\mathbf{W}}\mathbf{Q}_i{}^T = \mathbf{I} \quad \text{and} \quad \tilde{\mathbf{W}}^{-1/2}\mathbf{U}_i\tilde{\mathbf{W}}^{-1/2} = \mathbf{K}_i\mathbf{D}_i\mathbf{K}_i{}^T \tag{20}$$

with $\mathbf{D}_i$ a diagonal matrix (GANTMACHER 1960, pp. 310–314). The transformation $\mathbf{Q}_i\mathbf{C}_{ii}\mathbf{Q}_i{}^T = \mathbf{X}_{ii}$ carries (19) into

$$\frac{d\mathbf{X}_{ii}}{dt} \simeq -\mathbf{X}^2{}_{ii} + \mathbf{D}_i \ . \tag{21a}$$

From the initial condition $\mathbf{X}_{ii}(0) = \mathbf{0}$, $\mathbf{X}_{ii}(t)$ is evidently diagonal for all time, even under changing selection pressures for which $\mathbf{Q}_i$ would be time dependent. Then, for any subsequent initial condition, $\mathbf{X}_{ii}(t_1) = \mathbf{Q}_i\mathbf{C}_{ii}(t_1)\mathbf{Q}_i{}^T$ equation (21a) has the solution

$$\begin{aligned}\mathbf{X}_{ii}(t) \simeq \mathbf{D}_i{}^{1/2} - (&[\mathbf{D}_i{}^{1/2} - \mathbf{X}_{ii}(t_1)]^{-1}\exp\{2\mathbf{D}_i{}^{1/2}(t-t_1)\} \\ &+ (1/2)\mathbf{D}_i{}^{-1/2}[\mathbf{I}-\exp\{2\mathbf{D}_i{}^{1/2}(t-t_1)\}])^{-1} \ .\end{aligned} \tag{21b}$$

The rates of equilibration of the different components of variation at locus i are given by the elements of the diagonal matrix $2\mathbf{D}_i{}^{1/2}$, which from (20) are the eigenvalues of $2(\tilde{\mathbf{W}}^{-1}\mathbf{U}_i)^{1/2}$ and similar matrices. The equilibrium contribution to the genetic covariance matrix from locus i is obtained from the inverse transformation of the first term, and using (20) this is found to be

$$\mathbf{C}_{ii} \simeq \tilde{\mathbf{W}}^{1/2}\sqrt{\tilde{\mathbf{W}}^{-1/2}\mathbf{U}_i\tilde{\mathbf{W}}^{-1/2}}\ \tilde{\mathbf{W}}^{1/2} \ , \tag{21c}$$

where the matrix square roots are taken to be positive semidefinite. Then (17)

becomes $\mathbf{C}_{ij} \simeq \mathbf{C}_{ii}\tilde{\mathbf{W}}^{-1}\mathbf{C}_{jj}/r_{ij}$. The dynamics of the total genetic covariance matrix follow the formula

$$\mathbf{G}(t) \simeq 2 \sum_{i=1}^{n} \mathbf{Q}_i^{-1}\mathbf{X}_{ii}(t)(\mathbf{Q}_i^{-1})^T . \tag{22a}$$

For a single polygenic character with $\mathbf{W}+\mathbf{P} = w^2 + \sigma_z^2$, $\mathbf{G}+\mathbf{E} = \sigma_g^2 + \sigma_e^2$ and $\mathbf{U}_i = u_i$ starting from a homozygous population at $t_1 = 0$, genetic variance from mutation accumulates according to

$$\sigma_g^2(t) \simeq 2 \sum_{i=1}^{n} \sqrt{u_i(w^2+\sigma_e^2)} \left(1 - \frac{2}{1+\exp\{2t\sqrt{u_i/(w^2+\sigma_e^2)}\}}\right) . \tag{22b}$$

The more mutable loci (with higher values of u_i) contribute more to the equilibrium genetic variance and have the faster rates of equilibration. The time scale of equilibration for the genetic variance of a weakly selected character with n_E equally mutable loci [$w^2 >> \sigma_z^2$ and $u_i = \sigma_m^2/(2n_E)$, where σ_m^2 is the total mutational variance for the character] is about

$$\tau = \frac{1}{2}\sqrt{\frac{n_E\,\sigma_e^2}{L\sigma_m^2(1-h^2)}} \tag{22c}$$

generations, where $L \simeq \sigma_z^2/(2w^2)$ is the selective load in a large population under weak stabilizing selection with mean phenotype at the optimum (LANDE 1976). For evaluation of τ from data cited in the discussion, note that the heritability, $h^2 = \sigma_g^2/\sigma_z^2$, of most morphological characters in large stable populations is between about 0.1 and 0.6 (FALCONER 1960, Chapter 10). With loci of unequal mutability, the rate of equilibration is initially faster but ultimately slower than in the case of equally mutable loci. Selection on pleiotropic effects will further alter the evolution of each locus (eq. 21), but the time scale for changes in the genetic covariances between traits, G_{ij}, may be on the same order of magnitude as for the genetic variance of a particular character, G_{ii} (eq. 22a).

DISCUSSION

Genetic correlations between characters in a large randomly mating population arise from pleiotropy and linkage disequilibrium created by selection. When selection on polygenic variation is weak compared to twice the harmonic mean recombination rate between loci with interacting fitnesses, pleiotropic mutation is the major factor maintaining genetic correlations between traits, with linkage disequilibrium contributing relatively little (eq. 18). The genetic covariance matrix of the characters is then determined by a balance between the patterns of pleiotropic mutation and multivariate selection on the phenotype. This may apply to most morphological characters in higher organisms that have an "effective" (or minimum) number of loci, n_E, of about 5 to 10 spread throughout the genome (WRIGHT 1952, 1968, Chapter 15; 1969, pp. 72–105; ROBERTSON 1968); natural selection on morphological characters (including indirect selection acting through phenotypically correlated traits) is usually not very strong, with

phenotypic loads, L, ranging from a few to several percent (JOHNSON 1976, pp. 171–182).

The low probability of linkage between functionally related loci in eukaryotes (*versus* prokaryotes) is made possible by the evolution of separate control elements for each locus and has subsequently evolved by two mechanisms. The first is chromosomal rearrangement, especially the fixation of inversions, fusions and fissions; of lesser importance in outbreeding populations are reciprocal translocations. This process is so slow that even diverse mammals (which, for vertebrates, have relatively rapid rates of chromosomal rearrangement) are expected to show many homologous gene sequences preserved from their common ancestors. The second mechanism, which is also slow and probably no longer operates in higher vertebrates, is polyploidy followed by random loss or change of function at some of the duplicated loci. This would tend to scatter the loci influencing a given trait among different chromosomes, and would unlink previously linked genetic functions by complementary inactivations or changes in duplicated blocks of genes (OHNO 1970; BODMER 1975; LALLEY, MINNA and FRANKE 1978; LANDE 1979b).

The strongest force opposing the positional randomization of functionally related loci is tandem duplication. From the number of known cases (HARRIS 1970; OHNO 1970), it is apparent that tandem duplication and differentiation sometimes is more rapid than chromosomal rearrangement and polyploidy. Although tight linkage between genes with interacting fitnesses can produce substantial linkage equilibrium (eq. 17), mere duplication of genes is not sufficient for linkage to influence the genetic covariance between phenotypic traits. Not only must the loci be tightly linked, but they must be differentiated in the array of phenotypic effects they produce. By use of the same transformation in (20) for each locus, and equations in LANDE (1976), it can be shown that the recombination rates between identical duplicate genes (which may be expressed to different degrees) do not influence the genetic covariances maintained between traits.

At the opposite extreme, when the loci affecting two characters have become entirely distinct by the chromosomal processes discussed above, any genetic correlation must be due to linkage disequilibrium. Consider two genetically distinct characters with n_1 and n_2 loci (or "segregating factors"), respectively. For each character, the loci are assumed to be of equal effect and unlinked so that in a randomly mating population they are approximately in linkage equilibrium. Then, if n^* ($\leq$ minimum of n_1 and n_2) pairs of loci for the two characters are linked, the genetic correlation between the traits, γ, due entirely to linkage disequilibrium, has the upper bound $\gamma \leq n^*/\sqrt{n_1 n_2}$. Thus, linkage may play a significant role in maintaining the genetic correlations between characters only if a substantial fraction of the effective number of loci influencing two charcters under correlated selection are tightly linked. This conclusion does not depend on the degree of dominance, the tightness of linkage or the particular mutation model; its validity rests only on additivity of phenotypic effects between loci. Numerical analysis of equations (16) for this case demonstrated that under weak correlated selection on the characters (*cf.*, condition 18), the upper bound on γ is closely approached only with very tight linkage between the loci affecting

genetically distinct traits. Further numerical calculations for a variety of pleiotropic mutation, selection and recombination schemes confirmed that the general dynamic equations (16) for the genetic covariation have a unique equilibrium, which is globally and asymptotically stable.

Observed rates of production of additive genetic variance by spontaneous mutation in quantitative traits average roughly 10^{-3} times the environmental variance for characters of maize, mice and Drosophila. Total mutation rates are often in excess of 10^{-2} per gamete per character per generation, with extensive pleiotropy (EAST 1935; RUSSELL, SPRAGUE and PENNY 1963; MUKAI 1964; MUKAI *et al.* 1972; HOI-SEN 1972). These mutation rates are sufficient to maintain typical levels of heritable variation in large populations under stabilizing selection (LANDE 1976). The highly mutability of metrical traits results because (1) they are usually polygenic and (2) the rate of mutations declines exponentially with the magnitude of their effect (GREGORY 1965, 1966), so that spontaneous quantitative mutations for typical morphological characters are orders of magnitude more frequent than the usual single-locus rates for major mutants. Unequal crossing over in highly repetitive tandem gene families may also contribute to the high mutability of quantitative characters (FRANKHAM, BRISCOE and NURTHEN 1978). (For further review of quantitative mutation, see WRIGHT 1977, Chapter 5).

The virtual ubiquity of pleiotropic genes with overlapping specificities and the high mutability of polygenic traits indicate that complex genetic systems are sufficiently flexible to show substantial changes in the covariance between traits in response to a change in the regime of selection. With realistic mutation and selection parameters, as above, the time scale for changes in the genetic covariance structure may be as short as a few thousand generations (eq. 22 and numerical analysis of 16). Although a sudden alteration of the pattern of stabilizing selection can produce a geologically rapid change in the genetic covariances between characters, for some characters in natural populations the genetic structure is rather stable during long periods of time (*e.g.*, LANDE 1979a) due to conservation of the patterns of mutation and stabilizing selection around a (moving) optimum phenotype (eq. 14a).

I thank J. F. CROW, A. GIMELFARB, R. C. LEWONTIN, T. NAGYLAKI and the reviewers for discussion and criticism. This work was sponsored by Public Health Service grants GM-07131 and GM-22038 and is paper No. 2277 from the Laboratory of Genetics, University of Wisconsin, Madison.

LITERATURE CITED

APOSTOL, T. M., 1962 *Calculus*, Vol. 2. Blaisdell Publ. Co., Waltham.

BADER, R. S. and J. S. HALL, 1960 Osteometric variation and function in bats. Evolution **14**: 8–17.

BERG, R., 1960 The ecological significance of correlation pleiades. Evolution **14**: 171–180.

BODMER, W. F., 1975 Analysis of linkage by somatic cell hybridization and its conservation by evolution. pp. 53–61. In: *Chromosome Variations in Human Evolution.* Edited by A. J. BOYCE. Halsted Press, New York.

BRAVER, N. B., 1956 *The Mutants of* Drosophila melanogaster *Classified According to Body Parts Affected.* Carnegie Inst. Wash. Publ. No. 522A.

CASPARI, E., 1952 Pleiotropic gene action. Evolution **6**: 1–18.

COCHRAN, W. G., 1951 Improvement by means of selection. Proc. 2nd. Berkeley Symp. Math. Stat. and Prob. pp. 449–470.

DOBZHANSKY, TH. and A. M. HOLTZ, 1943 A reexamination of the problem of manifold effects of genes in *Drosophila melanogaster.* Genetics **28**: 295–303.

EAST, E. M., 1935 Genetic reactions in Nicotiana. III. Dominance. Genetics **20**: 443–451.

FALCONER, D. S., 1960 *Introduction to Quantitative Genetics.* Ronald Press, New York.

FISHER, R. A., 1930 *The Genetical Theory of Natural Selection.* Clarendon Press, Oxford.

FLEMING, W. H., 1979 Equilibrium distributions of continuous polygenic traits. S.I.A.M. J. Appl. Math **36**: 148–168.

FRANKHAM, R., D. A. BRISCOE and R. K. NURTHEN, 1978 Unequal crossing over at the rRNA locus as a source of quantitative genetic variation. Nature **272**: 80–81.

GANTMACHER, F. R., 1960 *The Theory of Matrices,* Volume One. Chelsea Publ. Co., New York.

GAUL, H., 1961 Use of induced mutations in seed-propagated species. pp. 206–251. In: *Mutation and Plant Breeding.* Natl. Acad. Sci.—Natl. Res. Council Publ. 891, Washington, D.C.

GREEN, E. L., 1962 Quantitative genetics of skeletal variations in the mouse. II. Crosses between four inbred strains. Genetics **47**: 1085–1096. ——, 1975 *Biology of the Laboratory Mouse,* Second Edition. Dover, New York.

GREGORY, W. C., 1965 Mutation frequency, magnitude of change and the probability of improvement in adaptation. Radiation Botany **5** (Supp.): 429–441. ——, 1966 Mutation breeding. pp. 189–218. In: *Plant Breeding.* Edited by K. J. FREY. Iowa State Univ. Press, Ames.

GRÜNEBERG, H., 1963 *The Pathology of Development.* John Wiley and Sons, New York.

HADORN, E., 1956 Patterns of biochemical and developmental pleiotropy. Cold Spr. Harb. Symp. Quant. Biol. **21**: 363–373.

HARRIS, H., 1970 *The Principles of Human Biochemical Genetics.* North-Holland Publ. Co., Amsterdam and London.

HAZEL, L. N., 1943 The genetic basis of constructing selection indexes. Genetics **28**: 476–490.

HOI-SEN, Y., 1972 Is sub-line differentiation a continuing process in inbred strains of mice? Genet. Res., Camb. **19**: 53–59.

JOHNSON, C., 1976 *Introduction to Natural Selection.* Univ. Park Press, Baltimore.

KENDALL, M. G. and A. STUART, 1973 *The Advanced Theory of Statistics,* Vol. 2. Inference and Relationship. (Third edition.) Hafner Publ. Co., New York.

KIMURA, M., 1965 A stochastic model concerning the maintenance of genetic variability in quantitative characters. Proc. Natl. Acad. Sci. U.S. **54**: 731–736.

KURTÉN, B., 1953 On the variation and population dynamics of fossil and recent mammal populations. Acta Zool. Fennica **76**: 1–122.

LALLEY, P. A., J. D. MINNA and U. FRANCKE, 1978 Conservation of autosomal synteny groups in mouse and man. Nature **274**: 160–163.

LANDE, R., 1976 The maintenance of genetic variability by mutation in a polygenic character with linked loci. Genet. Res., Camb. **26**: 221–235. ——, 1977 The influence of the mating system on the maintenance of genetic variability in polygenic characters. Genetics **86**: 485–498. ——, 1979a Quantitative genetic analysis of multivariate evolution, applied to brain:body size allometry. Evolution **33**: 402–416. ——, 1979b Effective deme sizes during long-term evolution estimated from rates of chromosomal rearrangement. Evolution **33**: 234–251.

LINDSLEY, D. L. and E. H. GRELL, 1968 *Genetic Variations of* Drosophila melanogaster. Carnegie Inst. Wash. Publ. No. 627.

MUKAI, T., 1964 The genetic structure of natural populations of *Drosophila melanogaster*. I. Spontaneous mutation rates of polygenes controlling viability. Genetics **50**: 1–19.

MUKAI, T., S. I. CHIGUSA, L. E. METTLER and J. F. CROW, 1972 Mutation rate and dominance of genes affecting viability in *Drosophila melanogaster*. Genetics **72**: 335–355.

OHNO, S., 1970 *Evolution by Gene Duplication*. Springer-Verlag, New York.

OLSON, E. C. and R. L. MILLER, 1958 *Morphological Integration*. Univ. of Chicago Press, Chicago.

PEARSON, K., 1903 On the influence of natural selection on the variability and correlation of organs. Phil. Trans. Roy. Soc. Lond. A. **200**: 1–66.

ROBERTSON, A., 1968 The spectrum of genetic variation. pp. 5–16. In: *Population Biology and Evolution*. Edited by R. C. LEWONTIN. Syracuse Univ. Press, Syracuse.

ROMER, A. S., 1966 *Vertebrate Paleontology*. Univ. of Chicago Press, Chicago.

RUSSELL, W. A., G. F. SPRAGUE and L. H. PENNY, 1963 Mutations affecting quantitative characters in long-time inbred lines of maize. Crop Science **3**: 175–178.

SINGH, R. S., 1976 Substrate-specific enzyme variation in natural populations of *Drosophila pseudoobscura*. Genetics **82**: 507–526.

SPRAGUE, G. F., W. A. RUSSELL and L. H. PENNY, 1960 Mutations affecting quantitative traits in the selfed progeny of doubled monoploid maize stocks. Genetics **45**: 855–866.

STERN, C. and C. TOKUNAGA, 1968 Autonomous pleiotropy in *Drosophila*. Proc. Natl. Acad. Sci. U.S. **60**: 1252–1259.

WRIGHT, S., 1934 The results of crosses between inbred strains of guinea pigs, differing in number of digits. Genetics **19**: 537–551. ——, 1952 The genetics of quantitative variability. pp. 5–41. In: *Quantitative Inheritance*. Edited by E. C. R. REEVE and C. H. WADDINGTON. Her Majesty's Stationery Office, London. ——, 1968 *Evolution and the Genetics of Populations*, Vol. I. Genetic and Biometric Foundations. Univ. of Chicago Press, Chicago. ——, 1969 *Evolution and the Genetics of Populations*, Vol. II. The Theory of Gene Frequencies. Univ. of Chicago Press, Chicago. ——, 1977 *Evolution and the Genetics of Populations*, Vol. III. Experimental Results and Evolutionary Deductions. Univ. of Chicago Press, Chicago.

Corresponding editor: W. J. EWENS